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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/994,440	11/26/2001	Melissa K. Carpenter	091/010C	1921
22869	7590	05/03/2005	EXAMINER	
GERON CORPORATION 230 CONSTITUTION DRIVE MENLO PARK, CA 94025			TON, THAIAN N	
			ART UNIT	PAPER NUMBER
			1632	

DATE MAILED: 05/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/994,440

Applicant(s)

CARPENTER ET AL.

Examiner

Thaian N. Ton

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 10 January 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-15 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-15 is/are rejected.
- 7) ☒ Claim(s) 2 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

### DETAILED ACTION

Applicants' Amendment, filed 9/15/04, has been entered. Claim 1 has been amended. Claims 1-15 are pending and under current examination.

#### *Specification*

The amendment filed 1/10/05 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

1. The amendment to paragraph 16, lines 8-11 recites that the medium can be conditioned by culture with another cell population, or a synthetic mixture of factors that promote growth of the hpPS while inhibiting differentiation.

2. The amendment to p. 16, lines 26-32 state that, "It is recognized that the beneficial effects of fibroblast conditioned medium are derived from soluble factors produced by the embryonic fibroblasts, and that synthetic mixtures having similar components in various combinations may also be beneficial."

Applicants point to specific portions of the priority document, 60/213,739, for where support for these amendments may be found. Careful inspection of the '739 application fails to provide specific support for these amendments. The Examiner points specifically to page 22, lines 22-25 with regard to these amendments. This section of the '739 document states that, "It has also been found that hPS cells

plated in the absence of fresh feeder cells benefit from being cultured in a nutrient medium. The medium will generally contain the usual components to enhance cell survival, including isotonic buffer, essential minerals, and either serum or serum replacement of some kind. Also beneficial is a medium that has been conditioned to supply some of the elements provided by feeder cells. Conditioned medium can be prepared by culturing irradiated primary mouse embryonic fibroblasts (or another suitable cell preparation) ....” This fails to provide specific support for the following parts of the amendment: the amendment states that the medium can be cultured by “another cell population”, the priority document refers to a suitable cell population. There is no recitation in the priority document of any synthetic mixture(s) of factors that promote the growth of hPS cells. The priority document state that the medium, which contains components (not a synthetic mixture) that enhance cell survival, not growth. Finally, the amendment recites that the beneficial effects of fibroblast-conditioned medium are derived from soluble factors produced by embryonic fibroblasts. The priority document merely states that conditioned medium can be prepared by culturing irradiated mouse fibroblasts, there is no specific disclosure of these factors being soluble.

Applicant is required to cancel the new matter in the reply to this Office Action.

***Claim Objections***

Claim 2 is objected to because of the following informalities: the claim appears to have a typographical error, reciting "s" in line 1 (prior to the term *culturing*). Appropriate correction is required.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 20 of copending Application No. 10/330,873. This rejection is maintained for reasons of record. Applicants state that they will address this issue upon determination that the claims in the instant application are otherwise patentable. See p. 8 of the Response, filed 9/15/04.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 7, 8, 10-13 and 15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 19 and 20 of copending Application No. 10/235,094. This rejection is maintained for reasons of record. Applicants state that they undertake to address this issue upon determination that the claims in the instant application are otherwise patentable. See p. 8 of the Response, filed 9/15/04.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 1 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 33 and 38 of copending Application No. 09/859,291. This rejection is maintained for reasons of record. Applicants state that they undertake to address this issue upon determination that the claims in the instant application are otherwise patentable. See p. 8 of the Response, filed 9/15/04. Applicants' willingness to address this issue is noted, but this rejection may not be held in abeyance because the '291 application has an earlier filing date.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1 and 4 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 4 of copending Application No. 10/087,473. This rejection is maintained for reasons of record. Applicants state that they undertake to address this issue upon determination that the claims in the instant application are otherwise patentable. See p. 8 of the Response, filed 9/15/04.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for producing differentiated cells comprising a) isolating cells from the inner cell mass of a human blastocyst, b) forming colonies comprising undifferentiated cells from the isolated blastocyst cells, c) passaging and culturing cells from the colonies in a culture in the absence of feeder cells in a culture environment that comprises an extracellular matrix and a fibroblast-conditioned medium, and d) differentiating the cultured cells into a population comprising lineage restricted cells or terminally differentiated cells, does not reasonably provide enablement for methods for producing differentiated cells by



isolation of cell from the ICM of a human blastocyst, forming colonies comprising undifferentiated cells from the isolated blastocyst cells, and passaging and culturing the cells from the colonies on an extracellular matrix in an environment that is essentially free of feeder cells, culturing the passaged cells in a culture environment in a medium conditioned by feeder cells, and differentiating the cultured cells into a population comprising lineage restricted cells or terminally differentiated cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The amendment to the claims is not found to be enabling because it does not recite that the cells are cultured on extracellular matrix and in a medium conditioned by fibroblast feeder cells. The recitation of "feeder" cells for conditioning the medium is not enabling because of the art-recognized unpredictabilities in the culturing of primate embryonic stem cells, the lack of teachings or guidance provided by either the specification or the art with regard to factors that a particular feeder cell line would provide in order to maintain ES cells in an undifferentiated state, and the working examples provided by the specification, which exemplify that only fibroblasts would be suitable for being used to condition the medium.

In the Office action mailed 1/16/04, pages 7-12, the Examiner has set forth both the state of the art of culturing ES cells, and the unpredictabilities in



maintaining such cells in an undifferentiated state. The Examiner cited Thomson, as well as working examples from the instant specification, which support that only fibroblast cells are enabled for conditioning medium to maintain undifferentiated ES cells. In short, Thomson (cited previously) teach that without embryonic fibroblast feeder layers, primate pluripotent stem cells will either differentiate or die. The specification also supports this finding (see p. 3, lines 30-31). The specification is enabling only for culturing the described pPS cells in the presence of an extracellular matrix and in the presence of fibroblast-conditioned medium. The working examples in the specification show that conditioned medium from fibroblast cells are capable of maintaining ES cells in an undifferentiated state when cultured on an extracellular matrix. However, cells that are not of fibroblast origin fail to do this, and the ES cells subsequently differentiate. See Example 11, and Figure 1. Lim (also cited previously) provide specific teachings with regard to the proteome analysis of conditioned medium from mouse embryonic fibroblast feeder layers to characterize the environment that supports the growth of undifferentiated human ES cells, and to identify factors critical for their independent growth. In particular, they conclude that it is yet unknown what factors fibroblast feeders provide to maintain ES in an undifferentiated state.

Accordingly, in view of the teachings of the state of the art with regard to the culturing of primate stem cells, the unpredictable nature of culturing undifferentiated primate stem cells, the lack of direction or guidance provided by

the specification for culturing the undifferentiated pPS cells under any feeder-free condition, other than the exemplified condition, wherein the culturing of the pPS cells require an extracellular matrix protein and fibroblast-conditioned medium in order to maintain the hES cells in an undifferentiated state, it would have required undue experimentation for one of skill in the art to carry out the claimed methods.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson in view of Gearhart (both cited previously). This rejection is maintained for reasons of record.

Applicants argue that Thomson refers to primate embryonic stem cells, and Gearhart relate to human embryonic germ cells. Thomson teaches that primate ES cells must be grown on feeder layers in order to keep them from differentiation. Applicants point to Gearhart showing that the hEG cells depend upon the presence of a ligand that binds to a receptor that associated with glycoprotein 130 in combination with a growth factor, and the working examples of Gearhart disclose culturing the hEG cells in a layer of STO cells. Applicants argue that ES cells are from blastocysts, and EG cells are obtained from the gonadal ridge of a more developed fetus, and that there is no teaching/suggestion with regard to what, if any, techniques proposed for culturing hEG cells can be adapted to culture ES cells. See p. 8 of the Response.

Applicants' arguments are not found to be persuasive. Thomson teaches human ES cells. Gearhart teach culture conditions wherein human EG cells can be cultured in feeder free conditions by culturing them on an extracellular matrix (col. 9, lines 57-67). Applicants point to specific culture conditions that Gearhart teach, but this is not the only contemplated condition taught in the Gearhart patent. The prior rejection of record is maintained because Gearhart provide conditions wherein pluripotent human embryonic cells can be maintained in an undifferentiated state,

and further, they teach the limitations of the claims. It is reiterated that the claims are directed to methods of maintaining human embryonic cells in an undifferentiated states. Although Gearhart teach human embryonic germ cells, and not embryonic stem cells (as taught by Thomson), both of these cell types share many of the same properties, including being highly pluripotent, and capable of differentiating into multiple cell types. Therefore, it would have been *prima facie* obvious for one having ordinary skill in the art at the time the invention was made, to use any of the various known conditions of maintaining and differentiating embryonic stem cells, such as those taught by Gearhart, for culturing human ES cells. In this case, one having ordinary skill in the art would have been motivated to substitute feeder-free conditions with an extracellular matrix in order to obtain a pure population of stem cells and cultures free from contamination of feeder cells. The art teaches that both EG and ES cells are phenotypically similar, and their greatest difference is their source. There would have been a reasonable expectation of success, given the results of both Thomson and Gearhart, to use the methods taught by Gearhart to culture the ES cells, as taught by Thomson, given the art-recognized similarity of both ES and EG cells.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

***Conclusion***

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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